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1. Your reference WPM/P7080GB

2. Patent application number *(The Patent Office will fill in this part)* 28 NOV 1997 **9725346.2**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

MEDEVA EUROPE LIMITED
10 St. James's Street
London SW1A 1EF

Patents ADP number *(if you know it)*

GB3352001

If the applicant is a corporate body, give the country/state of its incorporation United Kingdom

4. Title of the invention PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

5. Name of your agent *(if you have one)* W.H. BECK, GREENER & CO.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

W.H. BECK, GREENER & CO.
7 Stone Buildings
Lincoln's Inn
London WC2A 3SZ

Patents ADP number *(if you know it)* 323001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

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12. Name and daytime telephone number of person to contact in the United Kingdom: Watson P. McMunn - (0171) 405 0921

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PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

This invention relates to use of a polysaccharide gum such as Xanthan gum and hydroxypropylmethylcellulose (HPMC), particularly in the form of enemas for the treatment of inflammatory bowel disease (IBD), and to orally administrable and rectally/vaginally administrable compositions containing polysaccharide gum as a therapeutically active agent.

IBD covers chronic non-specific inflammatory conditions of the gastro-intestinal tract, of which the two major forms are Crohn's disease and ulcerative colitis. The aetiology of these diseases is uncertain. Many inflammatory mediators have been proposed including prostanoids, leukotrienes, platelet activating factor, cytokines, and free oxygen radicals. Although specific inhibitors of most of these have been tried in experimental models, the most effective drugs currently available for these diseases have a broad activity against inflammatory processes.

Crohn's disease is characterised by thickened areas of the gastro-intestinal wall, with inflammation extending through all layers, deep ulceration and fissuring of the mucosa, and the presence of granulomas. Affected areas may occur in any part of the gastro-intestinal tract, although the terminal ileum is frequently involved, and they may be interspersed with areas of relatively normal tissue. Fistulas and abscesses may develop. Symptoms depend on the site of disease but may include abdominal pain, diarrhoea, fever, weight loss and rectal bleeding.

In ulcerative colitis, disease is continued to the colon and rectum. Inflammation is superficial but continuous over the affected area and granulomas are rare. In mild disease, the rectum alone may be affected (proctitis). In severe disease ulceration is extensive and

much of the mucosa may be lost, with an increased risk of toxic dilatation of the colon, a potentially life-threatening complication.

Abdominal colectomy with mucosal proctectomy and ileal pouch-anal anastomosis is the preferred treatment for most patients with ulcerative colitis who require surgery. Pouchitis, the most common long-term complication of the procedure, occurs in up to 49% of patients at 10 years. Chronic pouchitis is distinguished from acute pouchitis by duration of symptoms for more than 4 weeks. The aetiology of pouchitis is unknown but it appears that both a history of ulcerative colitis and increased bacterial concentrations (relative to the normal ileum) are factors.

Currently, there is no satisfactory treatment for patients with chronic pouchitis who fail to respond to empiric antibiotic therapy. Although metronidazole is effective in some patients, long-term use is limited by concerns for neurotoxicity with peripheral neuropathy.

Numerous compounds have been examined in the last twenty years to find effective measures for the treatment of IBD. Such compounds include azathioprine, arsenicals, disodium cromoglycate, metronidazole, lignocaine, 5-aminosalicyclic acid (5-ASA), fish oils, thalidomide and cyclosporin. In EP-A-0351987, carbomer was proposed for treating IBD. The wide diversity of treatments, however, is an indication of the complexity and intransigence of this condition.

The inventors have now found that a polysaccharide (hydrogels/gums), in particular Xanthan gum and hydroxy propylmethyl cellulose (HPMC) and carboxymethylcellulose (CMC) in therapeutic amounts is effective for the treatment of IBD.

This is surprising, since the polysaccharide gums/hydrogels such as Xanthan gum, CMC and HPMC with cellulosic a backbone are normally thought to be inert. On the other hand, high doses of the polysaccharides can be used with minimal side effects.

Although Xanthan gum and other polysaccharide gums have been present as a thickening agent in enemas used to treat IBD (for example, Xanthan gum in WO-A-9603115), it was never realised that they also had pharmacologically active properties for treatment of the disease. Furthermore in EP-A-620012 (US-A-5518711), Xanthan gum is used at 0.15-0.6 w/v% in a X-ray contrast medium administered to the colon to detect Crohn's disease. Again, however, there is no report of it also treating the disease.

In US-A-5380522 a medicament of an anion-binding polymer and a hydrophilic polymer was used to alleviate irritable bowel syndrome. Xanthan gum was one of a number of compounds mentioned under anion-binding polymer, but is was not used in the examples.

Accordingly in a first aspect of the invention there is provided the use of a polysaccharide (hydrogel/gum) as a therapeutically active agent in the preparation of a medicament for the treatment or prophylaxis of IBD.

In a second aspect of the invention, there is provided a post-gastrically available delayed release oral (DRO) or rectally administrable pharmaceutical composition comprising a polysaccharide gum as a therapeutically active agent in an amount of treat inflammatory bowel disease, together with a pharmaceutically acceptable carrier or vehicle.

In a third aspect of the invention there is provided a rectally administrable or post-gastrically available delayed release oral (DRO) pharmaceutical composition comprising a polysaccharide gum as the sole therapeutically active agent

together with a pharmaceutically acceptable carrier or vehicle.

In a fourth aspect of the invention there is provided the use of a polysaccharide gum as the sole therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of IBD.

In yet another aspect of the invention there is provided a method for the treatment or prophylaxis of IBD comprising contacting the diseased mucosa of the gastro-intestinal tract with therapeutic amounts of a polysaccharide gum.

Suitable polysaccharide gums for use in the invention are the naturally occurring high molecular weight polysaccharide gums and chemically modified derivatives thereof. Examples are as follows:

Xanthan gum, Sodium carboxymethyl cellulose, Tragacanth, Methylcellulose, Sodium alginate, Hydroxypropylmethylcellulose, (HPMC), Karya gum, Methylethylcellulose, Soluble starch, Pectin, Propylene glycol alginate, Hydroxy ethyl cellulose, Guar gum, Carra geenan, Agar gum, and Gum acacia (arabic).

Preferably the polysaccharide is water soluble, but in some aspects it may be adapted to be water-insoluble. In a preferred form of the invention, the polysaccharide is Xanthan gum HPMC and CMC.

Xanthan gum (CAS registry no. 1138-66-2) is monographed at USP NF XVI p161 and is described as a high molecular weight polysaccharide gum produced by a pure-culture fermentation of a carbohydrate with Xanthomonas campestris. It contains D-glucose and D-mannose as the dominant hexose units, along with D-glucuronic acid and is prepared as the

sodium, potassium or calcium salt. Xanthan gum is commercially available from Systems Bio-Industries.

Another suitable polysaccharide gum is HPMC (CAS registry no. 9004-65-3), otherwise known as hypromellose. It is commercially available as Methocel® from The Dow Chemical Company. HPMC has been used as a coating for capsules, but the coating is soluble in gastric juices, and so would deliver the active in the capsule in the stomach. On the other hand, DRO compositions of the present invention pass through the stomach substantially unaltered and deliver their active ingredient (which is within the tablet, capsule etc.) typically to the ileum up to and including the colon (i.e. where the diseased mucosa is). HPMC has also been used as a swelling agent in tablets, but again the HPMC is not taught as therapeutically active for the treatment of IBD.

Carboxymethylcellulose (carmellose sodium) is a further suitable polysaccharide gum as shown by the examples hereinafter (CAS registry no. 9004-32-4).

Suitable pharmaceutically acceptable salts of the aforementioned polysaccharides are also within the scope of the invention and include alkali metals (e.g. sodium potassium) and alkaline earth metals (e.g. calcium or barium).

When a polysaccharide, such as Xantham gum or HPMC is present as the sole active agent, then no other therapeutically active agent such as 5-ASA or corticosteriods would be present.

Optionally, however, other therapeutic agents currently used or proposed for treating IBD can also be used sequentially in a different dosage form or concomitantly in the same dosage form as the polysaccharide gum. Examples of other such therapeutic agents are 5-ASA, immune modifiers

such as azathioprine, cyclosporine and FK506, corticasteroids such as prednisolone, budesonide and hydrocortisone, antibiotics such as metronidazole, ciprofloxacin, amoxicillin, tetracycline and sulphamethoxazole, and antidiarreals such as loperamide and codeine sulphate, and local anaesthetics such as lignocaine.

By IBD we mean Crohn's Disease and ulcerative colitis including ulcerative proctitis, ulcerative proctosigmoiditis, lymphocytic colitis, intractable distal colitis, ileocolitis, collagenous colitis, microscopic colitis, pouchitis, radiation colitis, and antibiotic-associated colitis. The invention has been found to be particularly useful in the treatment of IBD conditions (such as pouchitis and left-sided ulcerative colitis) normally refractive to conventional therapy.

The polysaccharide may be incorporated into a pharmaceutical composition to be administered either rectally, e.g. as an enema or foam enema, or orally, for example, in coated tablets or capsules as described below. Also, the polysaccharide may be formed into microgranules and coated, for example with Eudragit-L or S and contained within a capsule similarly coated. In all solid compositions it is preferable to include a disintegrant. Still further, the polysaccharide may be formulated in a number of dosage forms, e.g. uncoated or coated solid dosage forms for non-delayed release or delayed release oral administration, for example using different polymers in the Eudragit product range.

According to a preferred embodiment of the present invention, the pharmaceutical composition takes the form of an enema formulation such as a liquid or foam enema which is rectally administered to the lower colon. The enema formulations would comprise a polysaccharide gum such as Xanthan gum dissolved or dispersed in a suitable flowable carrier vehicle, such as deionised and/or distilled water.

The formulation can be thickened with one or more thickeners, can contain a buffer, and can also comprise an effective amount of a lubricant such as a natural or synthetic fat or oil, e.g. a tris-fatty acid glycerate or lecithin. Non-toxic non-ionic surfactants can also be included as wetting agents and dispersants. Unit doses of enema formulations can be administered from pre-filled bags or syringes. In the case of a pressurised enema formulation the carrier vehicle may also comprise an effective amount of a foaming agent such as *n*-butane, propane or *i*-butane, or the foaming agent/propellant could be held separately from the composition such as in a bag-in-can system. Enema foams may also comprise expanding agents and foam-stabilisers.

The viscosity of the enema is preferably 10,000 to 70,000 mPa.s more preferably 10,000 to 70,000 mPa.S and most preferably 10,000 to 40,000 mPa.S. The pH is preferably 3.5 to 7.5, preferably 6.5 to 7.5.

A dosage for a polysaccharide such as Xanthan gum in an enema or foam enema is 200mg to 2000mg, more preferably at least about 250mg (or 300mg to 400mg) to 2000mg, more preferably 250mg to 1650mg, more preferably still 400mg to 1650mg, more preferably still 550 to 1000mg in an aqueous or non-aqueous carrier. The volume of the enema is typically 50ml to 200ml preferably about 100ml. A suitable % w/w of Xanthan gum in an enema is (based on 100ml enema) is 0.2% to 2% w/w, more preferably 0.3% to 2% w/w, more preferably still 0.4% to 2% w/w, more preferably still up to 1.65% w/w, and still more preferably 0.55% to 1% foam enema. The volume of a foam enema is 20ml to 40ml. Based on the above preferred dosages, a suitable % w/w of Xanthan gum in a foam enema (based on 40ml foam enema) is 1% to 4.25% w/w, more prefgerably 1.4% to 2.5%. A buffer is preferably added to the enema or foam enema of Xanthan gum to stabilise the pH. When a buffer is used it increases the viscosity and as a result, the maximum % w/w of Xanthan gum that can be incorporated in the enema/foam enema is about 1.7% w/w.

Typically the viscosity grade of Xanthan gum used in a rectally administrable or DRO composition of the invention is 1,200 to 1,600 cP at 1% and 1% KCl.

Typically the viscosity grade of HPMC or CMC used in a rectally administrable or DRO composition of the invention is 3 to 100,000 CP. More particularly the grade of HPMC varies depending on the degree of hydroxypropoxy and methoxy substitution. Thus preferably the degree of methoxy substitution is 15 to 30%, more preferably 19 to 30% such as 19 to 24% and 27 or 28 to 30%. The degree of hydroxypropoxy substitution is preferably 2 to 15%, more preferably 4 to 12%, such as 7 to 12% or 4 to 7.5% The commercially available grades of HPMC sold under the trade mark Methocel® are as follows.

Product	% Methoxyl	% Hydroxypropoxyl	Viscosity cp	Relative Rate of Hydration
METHOCEL K Premium	19-24	7-12	3, 100, 4000, 15000, 100000	Fastest
METHOCEL E Premium	28-30	7-12	3, 5, 6, 15, 50, 4000	Next fastest
METHOCEL F Premium	27-30	4-7.5	50, 4000	Slower

The large range of viscosities allows a high dosage enema or foam enema of HPMC to be formed by using a low viscosity grade of HPMC (i.e. a higher dosage than Xanthan gum can be incorporated since the viscosity of the HPMC is less limiting). A suitable dosage of HPMC or CMC for a rectally administrable composition, such as an enema or foam enema is 0.2g to 20g, preferably at least 1g (or 2g) to 20g, more preferably still at least 1g to 10g, still more preferably 5g to 10g for some IBD disease states and at

least 1g (or 2g) to 5g for other IBD disease states. A suitable % w/w of HPMC or CMC in an enema or foam enema (based on 100ml) is 0.2% to 20% w/w, more preferably 1% or 2% w/w to 20%, more preferably to an upper limit of 10% w/w, more preferably still 5% to 10%. A suitable % w/w of HPMC or CMC in a foam enema (at 40ml) is 1% to 50% w/w, more preferably 2.5% to 25% w/w, such as at least 7.5% w/w.

In a further embodiment of the invention, the polysaccharide gum is administered to the small intestine or colon of a patient by oral ingestion of a post-gastric delayed release (DRO) unit dosage form such as a tablet or capsule, comprising an effective amount of polysaccharide gum which is enterically coated so as to be released from the unit dosage form in the lower intestinal tract, e.g. in the ileum and/or in the colon of the patient. Enteric coatings remain intact in the stomach, but dissolve and release the contents of the dosage form once it reaches the region where the pH is optimal for dissolution for the coating used.

A DRO formulation can also be achieved by coating a powder or microgranular formulation of a polysaccharide gum of the invention with coatings as mentioned above. The coated microgranules or material may then be compressed into tablets or packed into hard gelatin capsules suitable for oral administration. Suitable coatings and thicknesses to achieve this sustained release are also disclosed in EP-A-0572486 (incorporated herein by reference).

The DRO form may optionally also be formulated to give a sustained release of the polysaccharide gum. The delayed release can be obtained, for example, by complexing the polysaccharide gum with a polyacrylic acid derivative (a gum-polyacrylate complex) more particularly a gum-carbomer complex. Alternatively particles of the gum or gum complex could be incorporated into a hydrophobic matrix such as Gelucire™ (Gattefosse, France).

Aqueous film-coating technology is advantageously employed for the enteric coating of pharmaceutical dosage forms. A useful enteric coating is one that remains intact in the low pH of the stomach, but readily dissolves when the optimum dissolution pH of the particular coating is reached. This can vary between pH 3 to 7.5, preferably pH5 to 7, most preferably pH5.5 to 6.8 depending on the chemical composition of the enteric coating. The thickness of the coating will depend on the solubility characteristics of the coating material and the site to be treated.

By delayed release we mean that release is substantially post-gastrically, and by sustained release we mean that the total release of the polysaccharide (e.g. Xanthan gum) is slow and sustained over a period of time, as opposed to being released as a bolus.

The majority of the release will be targeted to the part of the small intestine or colon where the active disease is prevalent and this varies for Crohn's disease and ulcerative colitis. Thus typically for an enteric coated capsule, the enteric coating should dissolve in the pH of the jejunum (about pH5.5), ileum (about pH6) or colon (about pH6-7) so as to release the majority of the active from the jejunum to the colon - where most of the active disease is located in IBD. More particularly in the case of Crohn's disease most of the active disease is around the terminal ileum and so the enteric coating should dissolve about pH5.5 to 6. In the case of ulcerative colitis, the disease is mostly in the colon and therefore the enteric coating should dissolve about pH6 to 7, more particularly about pH6.8.

Preferably the unit dosage of polysaccharide, such as HPMC, CMC or Xanthan gum in the delayed release oral composition is 200mg to 2000mg more preferably at least about 250mg (or 300mg to 400mg) to 2000mg, such as 250mg to 1650mg, more preferably 400mg to 1650mg, more preferably

still 550mg to 1000mg. A suitable % w/w of polysaccharide such as HPMC, CMC or Xanthan gum in a DRO of the invention is 40 to 90% w/w, more preferably 60 to 80% w/w.

The above also is approximate to the total daily dosage and can be achieved by one or more unit dosages taken once, twice, three or more times daily. For example the total daily dosage is typically 200mg to 6000mg, preferably having a upper dosage limit of about 4000mg and a lower limit of about 400mg.

The DRO formulation can be provided in which an enteric coated capsule containing the polysaccharide gum has a coating , thickness of coating and dissolution profile described in EP-A-0097651 (the contents of which are incorporated herein by reference). Suitable coating include cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose or polyvinyl acetate phthalate but the preferred coating material is an anionic polymer, especially one having the dissolution profile specified in EP-A-0097651, optionally in admixture with a neutral insoluble but permeable polymer. The presently preferred anionic polymers are anionic carboxylic polymers, i.e. polymers in which the anionic groups are at least predominantly free carboxylic and/or esterified carboxylic groups. It is particularly preferred that the anionic polymers should be acrylic polymers and the presently most preferred polymers are partly methyl esterified methacrylic acid polymers such as poly(methacrylic acid, methyl methacrylate) in which the ratio of free acid groups to ester groups is about 1:1 ((e.g. those available from Röhm Pharma GmbH under the Trade Mark EUDRAGIT S). A neutral polymer coating, more specifically poly(ethylacrylate-methylmethacrylate) (e.g. Eudragit NE30D) may also be useful in some instances.

Examples of methacrylates (in the Eudragit range) for use as enteric coatings in accordance with the invention are as follows.

Chemical name	Trade name	CAS number
Poly(methacrylic acid, methyl methacrylate) 1:1	Eudragit L 100 Eudragit L 12.5 Euragit L 12.5 P	[25806-15-1]
Poly(methacrylic acid, ethyl acrylate) 1:1	Eudragit L 30 D-55 Eudragit L 100-55	[25212-88-8]
Poly(methacrylic acid, methyl methacrylate) 1:2	Eudragit S 100 Eudragit S 12.5 Eudragit S 12.5 P	[25086-15-1]

In general coating thicknesses of about 25 to 200 μm, and especially 75 to 150 μm, are preferred using about 3 to 25 mg, preferably 8 to 15 mg of acidic coating material per cm^2 of tablet or capsule surface. The precise coating thickness will however depend upon the solubility characteristics of the acidic material used and site to be treated.

In another preferred DRO or rectally administrable embodiment of the invention, sub 150μm particles of the polysaccharide gum or complex thereof (e.g. carbomer complex) is coated (partially or completely) or impregnated with a water insoluble anionic polymer. This prevents the formation of lumps and rather encourages the resulting hydrophobic particles of polysaccharide gum to disperse and coat the bowel wall when the contents of the DRO tablet or capsule are released. This technology is described in more detail in international application no. PCT/GB97/01847 (incorporated herein by reference).

By sub 150μm particles, we mean such that 100% of particles in the DRO will pass through a 150μm sieve. It is preferred that 100% of the hydrophillic carbomer particles pass a 100 μm sieve screen (i.e. they are sub 100 μm), more preferably at least 90%, especially at least 95%, of the

hydrophilic particles pass a 63 μm sieve screen, more preferably a 50 μm sieve screen. The precise particle size must be small enough to provide a composition with a suitable degree of hydrophobicity following coating with the anionic polymer. Preferred particle size may vary according to the nature and amount of the cation present in the complex and the nature and amount of the anionic polymer.

The amount of anionic polymer used will depend upon the nature and amount of the cation present in the salt, the nature of the impregnating anionic polymer, and the degree of hydrophobicity required. A suitable amount can be determined by simple experimentation but usually the anionic polymer will be present in an amount of 10 to 50%, preferably 20 to 40, more preferably 25 to 35 and especially about one third, based on the weight of the carbomer complex. Having regard to the small particle size the amount of polymer will be less than the theoretical amount required to coat the particles, and the swelling and dissolution of the carbomer will not be controlled by pH.

The polysaccharide particles are impregnated/ hydrophobised by milling and passing through a suitable sieve (as aforementioned), stirring the sieved particles into a mixture of e.g. isopropanol and water (solvent) and partly methyl esterified methacrylic acid polymer (e.g. Eudragit S100) at from 20 to 40% by weight of the polysaccharide particles (the solvent/coating solution having previously been agitated until clear), stirring then evaporating the solvent under vacuum at about 50-70° to leave coated polysaccharide particles. Thereafter the resulting powder can be filled into gelatin capsules ready for enteric coating.

The invention will now be described by way of the following examples.

Example 1 : Enema with HPMC.

947.6g of purified water is preserved with 2g of methyl and 0.4g propyl parabens. 50g (dry basis) of HPMC (Methocel E) low viscosity grade (50 cP) is dissolved under mechanical stirring at room temperature. The solution is degassed (air) under reduced pressure in an oven. A clear viscous enema is obtained pH : 6.9, viscosity (spindle 64, 1.5 rpm - 20°C on Brookfield DV 11): 4'000 m.Pa.s. The formation is packed in a bag-in-can canister or in an enema plastic pouch or in a PE bottle all having a 100g enema capacity delivery, thus delivering a full dose of 5'000mg HPMC.

Example 2 : Foam Enema Formulation with Xanthan gum.

14,871g of purified water containing 22g of dissolved methyl paraben and 2g of dissolved propyl paraben as preservatives were placed in a 20 litre Moltomat-Universal MMU 20 homogenizer. Then 435g of Xanthan gum Keltrol TF having a water content of 7.6% (form the Company Kelco) were dispersed in the preserved water under efficient homogenization and reduced pressure.

30g of unbleached lecithin were then added and dispersed under homogenization and reduced pressure. At this stage the pH of the viscous gel obtained was 6.3. A solution then made of 0.45 g sodium hydroxide pellets and 20g of water was added and dispersed under reduced pressure. The pH then was 6.93. Finally 155g of Polysorbate 80 (non-ionic surfactant) and 4g of Citral (perfume) were added and dispersed under reduced pressure.

The final foam enema appeared as a slightly hazy gel, having a pH of 7.04 and a viscosity of 40'000 mpa.s at 20°C as measured using a Brookfield DV II viscometer (1.5 rpm, spindle 63).

A foam enema was then produced using this formulation by adding 2.2g of n-butane per 100g of the above formulation in a pressurised mixing unit and the mixture was then filled into bag-in-can aerosol canisters. Each canister contained 23g of the mixture from which 21g of foam was delivered through a valve and an applicator, i.e. about 530 mg of Xanthan gum per delivered dose.

Liquid Enema Formulation : With Xanthan gum.

To 4,906g of purified water containing 10g of dissolved methyl paraben and 2g of dissolved propyl paraben used as preservatives, 58.95g of Xanthan gum Keltrol TF containing 6.7% water (i.e. 55g dry basis) was added in an homogenizer and dispersed under efficient homogenization under reduced pressure. The pH of the gel obtained was 6.05 and the viscosity was 7,500 mPa.s (22°C - 1.5 rpm-spindle 63 - Brookfield DV II). At this stage 23g of sodium citrate. $2H_2O$ was added as buffering agent. The pH went up to 7.15 and the viscosity 40,000 mPa.s measured as above. The formulation, which appears as a slightly hazy gel, was then packed into a bag-in-can canister equipped with a valve and an applicator and pressurised with nitrogen. If the bag of the bag-in-can system is filled with 104g of the formulation above then 100g of the formulation can be delivered through the valve and applicator corresponding to a dose of 1.1g of Xanthan gum.

Example 3

The enema of Example 2 was then given to patients. The patients were twenty adults who had previously undergone total colectomy with mucosal proctectomy and ileal J-pouch anal anastomosis for ulcerative colitis and who had active chronic pouchitis refractory to standard therapy. Patients had chronic pouchitis, as defined as continuous symptoms of pouchitis for more than 4 weeks and a Pouchitis Disease Activity Index (PDAI) score of at least 7 points on an 18

point scale. All patients had either failed or were intolerant to metronidazole as well as other commonly used treatments for pouchitis. Mucosal inflammation, determined by endoscopic examination, was limited to the pouch and did not extend into the ileum proximal to the pouch.

The demographics of the patients entered into the study are presented in Table 1. There were no significant differences in the age, gender distribution, smoking history, time since the diagnosis of ulcerative colitis, duration of pouch function, time since the first episode of pouchitis, duration of the current episode of pouchitis, or in the medications previously used for treatment of pouchitis. All patients had been on medication for pouchitis, previously, and one half of the patients were on concurrent treatment for chronic pouchitis (Table 2).

TABLE 1

PATIENT CHARACTERISTICS

Number of Patients	20
Age (mean)	40(18-62)
Number of Men:Women	12:8
Number of Cigarette Smokers, current:former:never	1:2:17
Years since diagnosis of Ulcerative colitis. Median (range)	9(3-32)
Months of pouch function. Median (range)	45(4-161)
Months since the first episode of pouchitis. Median (range)	42(3-151)
Months of current pouchitis episode. Median (range)	4(.8-151)

TABLE 2

THERAPY FOR POUCHITIS (20 PATIENTS)

Therapy	No. Of Patients Current	Previous
Antibiotics		
Metronidazole	3	16
Ciprofloxacin	6	15
Amoxicillin/clavulanic acid	1	6
Tetracycline	0	3
Trimethoprine/sulfamethoxazole	1	0
5-ASA		
Sulfasalazine	1	5
Oral mesalamine	0	5
Mesalamine enemas	0	3
Mesalamine suppositories	0	3
Corticoseroids		
Prednisone	1	7
Hydrocortisone enemas	0	5
Immune Modifiers		
Azathioprine	0	0
Cylcosporine	0	0
FK506	0	0
Antidiarrheals		
Loperamide	5	3
Codeine sulfate	0	1

TABLE 3

DISEASE ACTIVITY AT BASELINE AND COMPLETION OF TREATMENT WITH XANTHAN GUM ENEMA

	Baseline Median (range)	Completion Median (range)
Clinical Score	4(1,5)	3(0,4)*
Endoscopy Score	5(1,6)	4(1,6)
Histology Score	2(2,6)	2(2,6)
Total Score (PDAI)	11(7,16)	9(2,16)*

*$p<0.5$ for within-group change. Baseline vs completion (signed rank test with two missing values at completion filled in by overall (groups) Baseline values).

Three patients had to discontinue treatment because of worsening of symptoms, but none developed dehydration or required hospitalization. Three patients had cramping discomfort in the pouch after taking the enema. One of the patients who developed cramps discontinued it because of the discomfort. One patient developed right lower abdominal pain and the study medication was discontinued.

The initial or final endoscopic or histologic scores of the patients are shown in Table 3.

In conclusion six of the twenty patients discontinued therapy and nine of fourteen patients (64%) who completed the treatment improved (defined as a reduction in the PDAI score of 3 points or more). This is particularly surprising

in view of the fact that the patients were refractory to conventional therapy.

Example 5; Liquid enema with CMC

An enema of carboxymethylcellulose (CMC) was made up with: 3.5ml olive oil in 12.5% alcohol, 60ml water, 5mg sorbitol and 500mg CMC (medium viscosity). The CMC was obtained from Spectrum Chemical Manufacturing Corp. Gardena, California, USA.

The CMC enema was given to 20 patients with left-side ulcerative colitis, which was chronically active and generally refractive to other drugs. The demographic data of the patients' is shown in Table 5 and their current and previous drug therapy is shown in Table 6. Treatment consisted of one enema nightly for 4 weeks. Only four patients were receiving concomitant oral corticosteroids and/or salicylates during the study. Enema treatment was discontinued in 3 of the 20 patients.

Table 5

	Placebo (n = 2)	
	Median	**Range**
Age at entry (yr)	43	21-69
Duration of ulcertative colitis (yr)	2	0-24
Duration of current symptoms (days)	225	14-6570
Extent of disease (cm)	38	10-60
Initial DA1 score (range 0-12)	8	5-11
Initial HDAI score (range 0-4)	3	1-4
Sex (M/F)	10/10	

Table 6

	Placebo (n = 20) (%)
Current drug therapy	
No current treatment	20
Sallcyiates[a]	40
Steroids	15
Sallcyiates and steroids	25
Recently discontinued drug therapy[b]	
Topical steroids	30
Topical mesalamine	15
Previous drug therapy[c]	
Oral steroids	30
Topical steroids	45
Sulfasalazine	55
Olsalazine	10
Oral mesalamine	10
Topical mesalamine	40
Azathiophrine or 6-mercaptopurine	5

[a] - Salicylates are sulfasalazine, oisaiazine, and oral mesalamine.

[b] - Therapy discontinued ≤14 days before study entry.

[c] - Therapy discontinued >14 days before study entry.

The response to the CMC enema of the invention is shown in Table 7.

Table 7

	Placebo	p*
Disease activity Index	(n = 20)	
Clinical remission	1	0.90
Clinical improvement[b]	9	0.90
Clinical failure	11	0.90
Histological disease activity Index	(n = 18)	
Histological remission	1	0.77
Histological improvement[c]	7	0.77
Histological failure	11	0.77

p* - based on an extension of Fisher's Exact Test for ordered categories.

[b] - Clinical improvement includes clinical remission.
[c] - Histological improvement includes histological remission.

9 of 20 patients (45%) with left-sided ulcerative colitis who started the treatment, at 4 weeks showed clinical improvement. 9 of 17 (53%) patients who finished the treatment showed clinical improvement. This is a very significant result and is all the more surprising when one considers the refractory nature of the disease.

CLAIMS

1. A post-gastrically available delayed release oral (DRO) or rectally administrable pharmaceutical composition comprising a polysaccharide gum as a therapeutically active agent in an amount of treat inflammatory bowel disease, together with a pharmaceutically acceptable carrier or vehicle.

2. A DRO composition as claimed in Claim 1 wherein the dosage of the polysaccharide per unit dose is 200mg to 2000mg.

3. A DRO composition as claimed in Claim 2 wherein the dosage is 400mg to 2000mg.

4. A DRO composition as claimed in Claim 3 wherein the dosage is 550mg to 1000mg.

5. A DRO composition as claimed in any one of the preceding claims which is an enteric coated dosage form.

6. A DRO composition as claimed in Claim 5 wherein the enteric coating is adapted to release its contents anywhere from the jejunum to the colon.

7. A DRO composition as claimed in Claim 6 wherein the enteric coating is a partly methyl esterified methacrylic acid polymer or polyethylacrylate-methyl methacrylate.

8. A DRO composition as claimed in any one of the preceding claims wherein the dosage form is an enteric coated tablet or capsule or enteric coated microgranules.

9. A rectally administrable composition as claimed in Claim 1 which is an enema or foam enema.

10. A DRO or rectally administrable composition as claimed in any one of the preceding claims wherein the polysaccharide is present as the sole therapeutically active ingredient.

11. A DRO or rectally administrable composition as claimed in any one of the preceding claims wherein the polysaccharide is Xanthan gum.

12. A rectally administrable composition as claimed in Claim 11 wherein the dosage of the Xanthan gum is 0.2g to 2g.

13. A DRO or rectally administrable composition as claimed in Claim 12 wherein the dosage of the Xanthan gum is 0.4g to 2g.

14. A DRO or rectally administrable composition as claimed in any one of the preceding claims wherein the polysaccharide is HPMC or carboxymethylcellulose (CMC).

15. A rectally administrable composition as claimed in Claim 14 wherein the dosage of the HMPC or CMC is 0.2g to 20g.

16. A rectally administrable composition as claimed in Claim 15 wherein the dosage is 5g to 10g.

17. Use of polysaccharide gum in the preparation of a medicament for the treatment of inflammatory bowel disease.

18. Use as claimed in Claim 17 wherein the disease state is pouchitis.

19. Use as claimed in Claims 17 or 18 wherein the medicament is as claimed in any one of Claims 1 to 16.

20. The use of a polysaccharide gum as the sole therapeutically active agent in the manufacture of a medicament for the treatment or prophylaxis of inflammatory bowel disease.

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